



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Berger, A., et al.
Appl. No.: 10/089,658
Conf. No.: 6858
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Title: NUTRITIONAL COMPOSITION
Art Unit: 1615
Examiner: R. Berko
Docket No.: 112843-044

AFFIDAVIT UNDER 37 C.F.R. § 1.132

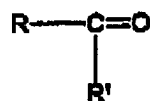
Sir:

I hereby state as follows:

1. My education and professional experience is attached with my curriculum vitae as Exhibit B.
2. I am one of the named inventors of the above-identified patent application and am therefore familiar with the inventions disclosed therein.
3. I have reviewed the outstanding Office Action dated June 16, 2005 pending against the above-identified patent application. In addition to considering the outstanding Office Action, I have reviewed the references cited therein, i.e., U.S. Patent No. 5,618,955 to Mechoulam et al. ("*Mechoulam*") and WO 96/37200 to Stordy et al. ("*Stordy*"), as well as the pending claims. I believe that the anticipation rejections of Claims 1 and 5 based on *Mechoulam* and Claims 1, 5, 16, 22 and 25 based on *Stordy* are incorrect and based on a misunderstanding of the references and the pending claims.
4. Independent Claim 1 is directed, in part, to a composition for oral administration comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises a long chain polyunsaturated fatty acid (LCPUFA) which is a polyunsaturated fatty acid of 16-28 carbon

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atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno, or wherein the precursor is a LCPUFA or derivative thereof of the general formula X:



wherein R is the alkenyl moiety of the LCPUFA of total chain length 16-28 carbon atoms with 2-6 double bonds, with the first double bond at the c-1, c-3 c6, c7, c9 c12 position, counting from the non carboxyl (methyl) part of the molecule; and where R' is selected from the group consisting of -H, lower alkyl, -OH, NH₂, NHCH₂CH₂OH, and an acid addition salt or complex thereof.

5. Independent Claim 16 recites, in part, a method of treating an anandamide-mediated ailment which comprises administering to a patient having an anandamide-mediated ailment an effective amount of a composition comprising a naturally occurring precursor that is metabolised to a compound having anandamide activity for use as a medicament, wherein the precursor comprises an LCPUFA which is a polyunsaturated fatty acid of 16-28 carbon atoms having from 2 to 6 double bonds, and having a moiety selected from the group consisting of methylated-, branched-, cyclic-, conjugated-, non-methylene interrupted-, epoxy-, furanoid-, hydroxyl-, allylic-, trans-, and seleno.

6. The term "anandamide activity" refers to an activity selected from the group which comprises an activity attributed to the drug 9-tetrahydrocannabinol (THC), as well as affects specific to anandamide and 1- and 2- monoarachidonylglycerol isomers (hereafter denoted AG), and unique from THC. It has been suggested that anandamide and AG activities are typically, but not necessarily, mediated by binding to the receptor class, known as CB1 and CB2 receptors. These anandamide activities include, but are not limited to: antinociception,

catalepsy and inhibition of locomotor activity *in vivo* and displacement of 9-tetrahydrocannabinol (THC), inhibition of adenylate cyclase, inhibition of calcium channels, activation of phospholipase A₂, release of intracellular calcium *in vitro* and inhibition of twitch response *ex vivo*.

7. It has been suggested that a family of NAEs and NAAs as well as sn-1 and sn-2 monoarachidonyl glycerides are agonists of anandamide receptors (here anandamide receptor refers to a receptor that anandamide might bind to, including CB1, CB2, non CB receptors) and elicit responses analogous to that elicited by anandamide. The chemical structures of NAEs and NAAs are based on fatty acids and depending on the specific fatty acids esterified they have been shown to have different activities. For example, whereas anandamide interacts with both the CB1 receptor of the central nervous system and the CB2 receptor of the immune system, palmitoylethanolamide may interact with the CB2 receptor but not the CB1 receptor and has an anti-inflammatory effect but no known neural effect.

8. As one skilled in the art, it was particularly surprising to me that a dietary precursor is selectively taken up by the central nervous system and selectively incorporated into the N-acyl ethanolamine ("NAE") pool to serve as a CB receptor-binding ligand. In addition, I believe that it is remarkable that a dietary precursor induces only a small change in the phospholipid acyl composition but induces a large change in the NAE composition.

9. *Mechoulam* is directed to synthetically produced polyunsaturated fatty acid amides and their derivatives (collectively "fatty acid amides") that are able to mimic the effect of naturally occurring anandamides in the brain and bind to the cannabinoid receptor. The fatty acid amides in *Mechoulam* are final synthesis products and can exhibit physiological activity. They are reported as being useful active ingredients in pharmaceutical compositions for treatment of inflammation, migraines, spasticity, glaucoma and multiple sclerosis.

10. In contrast to *Mechoulam*, Claim 1 recites, in part, a composition for oral administration that includes a precursor (e.g. intermediate) that is metabolized to form a compound having anandamide activity. For example, the precursor can be metabolized endogenously or within the body of a human being to form a compound having anandamide activity. Conveniently, *Mechoulam* is directed to a composition utilizing the end product that exhibits anandamide activity and not the precursor or intermediate capable of being metabolized to form a compound having anandamide activity as required by Claim 1. As one skilled in the art, I would not find *Mechoulam* to meet each element of Claim 1.

11. *Storzy* is directed to docosahexaenoic acid, which is a non-modified polyunsaturated acid. *Storzy* fails to disclose or suggest the compounds comprising the precursor long chain polyunsaturated fatty acids having the moieties detailed in independent Claims 1 and 16. As one skilled in the art, I would not find *Storzy* to meet each element of Claims 1 and 16.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18, United States Code, and that willful false statements may jeopardize the validity of this patent and any patent issuing therefrom.

Date: 13. October 2005

Allegio Hill

Print Name: Gayle Crouse Hill

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EDUCATION:

Bachelor of Arts (Psychology/Biology) 1972 Queen's University, Kingston, Canada
Master of Science (Nutrition) 1978 Guelph University, Guelph, Canada
Amino acid metabolism and gluconeogenesis in the developing piglet.
Doctorate, PhD (Nutrition) 1983 University of California, Davis, California
Factors involved in the regulation of nitrogen metabolism.

RESEARCH POSITIONS:

Postdoctorate 1984 Centre de Recherches sur la Nutrition, CNRS, Meudon, France
Medium chain triglyceride metabolism.
Assistant Professor 1987 Faculty of Health Sciences, McMaster University, Canada.
Lipids & Thrombosis.
Principle Scientist 1985-1990 Nestle Research Centre

TEACHING:

•University of Guelph 1977-1978, •University of California, Davis, 1979-1983, •UC Davis Cardiac Rehabilitation Program, Nutrition Advisor 1982-1983, •Dietary Nutrition Counsel 1987; •ETH Zurich, Graduate course in Nutrition, 1996-, •Michigan State/University of Guelph Joint Graduate course in Regulatory Affairs 2000-, •Nestlé Centre de Formation (Rive Reine) 1994-

LANGUAGES:

English, mother tongue.
French – fluent
German, Italian, Spanish – reading

WORK HISTORY

PRESENT POSITION

2003- Manager Food Issues, Public Affairs

Responsibilities: Nutrition and Labeling. Encourage development of programs in global markets. Develop communications materials on Nestlé programs, and activities. Liaise with WHO, governments and opinion leaders on nutrition issues. Coordinate with trade associations on non-competitive areas.

1999-2003 Manager, International Regulatory Affairs

Responsibilities: Nutrition and Labelling. •Key areas include nutrition policy, health claims, nutrition labelling, infant nutrition, fortification, dietary supplements, sports nutrition. •Explain issues, coordinate development of Nestlé positions with Business Units, Public Affairs, Zones and other internal groups. •Communicate industry positions in legislative and intergovernmental

fora - Codex, European Commission, WHO. • Advise Market contacts to aid in developing favorable national legislation. • Develop scientific and regulatory dossiers to support R&D and businesses in discussions with authorities.

PREVIOUS POSITION:

1990-1999 Head, Research Group, Lipids in Human Nutrition, Nestlé Research Centre.

Responsibilities: • Led group research activities and resources involved in healthful foods development related to dietary fat and antioxidant nutrition. • Identified and evaluated issues in lipid nutrition and developed research plans; human, animal and clinical trials, pan-European and governmental projects. • Liaised with the SBUs to recommend strategic alterations of foods, infant formulations, ice cream, food products, frying oils, pet foods, functional foods. • 6 Patents,

1985-1990 Chief Research Scientist, Lipids in Human Nutrition, Nestlé Research Centre
Responsibilities: Built research program in lipid science. Established research plan on essential fatty acids and eicosanoid research. Developed studies in biological systems, cell and tissue culture, animal trials. Hired and trained personnel.

NETWORK ACTIVITIES

ISDI (International Special Dietetics Foods Industries). Chair of Scientific and Technical Committee (Codex NGO). Coordinate input and develop and defend positions at Codex.

IDACE (European Dietetics Trade Association). Working Groups on: Infant Formula, Weaning Foods, Foods for Special Medical Purposes, Sports Foods, Innovation, Claims.

CIAA (Confederation of the Food and Drink Industries of the EU). Working Groups on: Health Claims, Nutrition Policy, Addition of Nutrients, Consumer Information.

Editorial board, International Journal of Vitamin and Nutrition Research

ILSI (International Life Sciences Institute):

EU linked Concerted Action on Functional Food Science in Europe. (Health Claims)

Two taskforces: Antioxidants, Dietary Fat.

Consultancies, Advisor to:

UK government (MAFF) grant evaluations for their Antioxidant Research Program

International Dairy Federation on nutrition matters related to milk fat

Nestlé Nutrition Foundation - grant evaluations

Canola Council of Canada on research program

Officer (elect) of the European Section of the American Oil Chemists' Society

Women in Science and Engineering (Swiss National Science Foundation)

Scientific Conferences, Organising Committee

5th International Prostaglandins and Essential Fatty Acids Congress

European Oil Chemists' Society 1998,99

International Society for Fat Research 1995, 1999

President, Graduate Students' Association, University of California, Davis 1980-83

Chair or Vice Chair, Graduate Students' Association, University of Guelph 1977-1978

Keynote and other Invited Lectures: • University of California, Davis; • University of Guelph; • Columbia University; • Lausanne University Hospital; • ETH Zurich; • International Society for Fat Research; • several AOCS Plenary Symposia; • International Society for the Study of Fatty Acids and Lipids (ISSFAL); • Dreiländer Symposium; • French Dietetics Association.

PUBLICATIONS

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3. Rodriguez M, Kiss S, Fink M, Dammelmair H, Turini M, Crozier G, Koletzko B. 2003 Plasma lipid fatty acid composition and metabolism of 13C-labeled linoleic acid in preterm infants fed a formula containing medium-chain triacylglycerols. J. Lipid Res. 44 41-48.
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5. Turini ME, Crozier GL, Donnet-Hughes A, Richelle MA. 2001 Short term fish oil supplementation improved innate immunity, but increased ex vivo oxidation of LDL in man - a pilot study. Eur. J. Nutr. 40 56-65
6. Berger A, Crozier G, Bisogno T, Cavaliere P, Imis S, Di Marzo V. 2001. Anandamide and diet: Inclusion of dietary arachidonate and docosahexaenoate leads to increased brain levels of the corresponding N-acyl ethanolamines in piglets. Proc. Natl. Acad. Sci. USA 98: 6402-6
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11. Crozier GL 1998 Long chain polyunsaturated fatty acid supplemented formula and antioxidant balance in preterm infants in Lipids in Infant Nutrition pp122-132 eds V. Huang and A. Sinclair. AOCs Press
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13. Turini M, and Crozier GL 1997. Increased fruit and vegetable consumption within the European Community: Potential Health Benefits. Office Fédéral De l'Éducation et de la Science, Euroscope vol 41:10-11
14. Campion CAC and Crozier GL. 1997 The Nestlé Research Centre - Department of Nutrition. British Nutrition Bulletin, Vol 22:119-122
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- 1996 AOCS Press
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